Remarks

Applicants have attended to minor informalities and changed the heading of the "BRIEF DESCRIPTION OF THE DRAWINGS" in accordance with the Examiner's suggestion. Applicants have amended the claims to particularly point out the subject matter which Applicants regard of the invention.

Claim Rejections Under 35 U.S.C. § 112

Amended Claims 1-3, 5, 11-13, 15, 17-24 and 26-29 have been rejection under 35 U.S.C. § 112, second paragraph. Applicants respectfully submit that as a result of the latest amendments the rejection under 35 U.S.C. § 112, second paragraph is now obviated.

Applicants have amended Claim 1 and 11 to include sequence identifiers. Applicants have amended Claims 1-3, 5 and 11 to clearly identify that the "functionally equivalent derivatives" will have about 67% homology to those nucleic acid and proteins defined within the Specification. Support for the inclusion of this limitation can be seen on page 2, lines 21-23 of the Specification, which show that the MDEG channel exhibits 67% homology to the ASIC channel. Further support for the use of homology percentage can be found in Table 1, page 6, of the Applicants' Specification, which illustrates the homology between the various acid sensitive ionic channels. No new matter has been added.

Applicants have amended Claim 21 to resolve antecedent basis issues. Applicants have further amended Claims 22 and 28 to remove the phrase "selected value", and to further point out that the current caused by contacting a substance is compared directly against a current measured

prior to contacting said substance. Support for amendments to Claims 22 and 28 can be found in the Brief Description of the Drawings of FIG. 5, as well as the figures themselves, which illustrates the measurement of a "baseline" current prior to contacting the cells with a substance, and the resulting current after the cells have been contacted. Applicants have amended Claim 26 to place the group in a proper Markush format, and Applicants have amended Claim 27 to remove any antecedent basis problems. Further, Applicants have attended to informalities in dependent Claims 12-13, 15, 17, 20, 23, 24 and 29, and as a result submits these claims are now in proper form and in condition for allowance.

Claim Rejection under 35 U.S.C. § 101 and 112, first paragraph

Claims 1-3, 5, 11-13, 15 and 17-24 and 26-29 have been rejected under 35 U.S.C. § 101.

This invention discloses the identification and molecular characterization of new proton-activated cationic channels referred to as "ASIC". More particularly, this invention concerns ASIC1 channels. These channels belong to the very large family of cationic channels.

The inventors have identified that those ASIC channels are activated by protons, as disclosed in experiments corresponding to FIG. 5.

The inventors have also identified that those channels are present in the sensory neurons and in the neurons of the central nervous system as disclosed in Northern blot analysis and the RT-PCR experiment (FIG. 7). Moreover, FIG. 8 discloses that said channel mRNA is well-expressed by the small neurons of the dorsal root ganglion that behave as nociceptors.

At the time of invention, pain caused by acids was interpreted as being mediated by the

cationic channels present at the level of the sensory neurons and which were activated by protons (Kirshtal and Pidoplichko, 1981, Neuroscience, 6, 2599-2601; Bevan and Geppetti, 1994, Trends Neurosci. 17, 509-512; Akaike, Krishtal and Mauyama, 1990, J. Neurophsiol., 63, 805-813). Nevertheless, in these purely electrophysiological publications, no indication was given on the molecular nature of the cationic channels that were implicated in pain caused by acids and no indication was given how to identify or characterize them.

As a consequence, the channels of this invention which correspond to proton-activated cationic channels present in the sensory neurons and in the neurons of the central nervous system, clearly illustrate a well-established utility thanks to their role in the mediation of pain caused by acids.

It is respectfully submitted that the Applicants have identified, characterized and provided electrophysical data for a new cationic channel (ASIC), which is the first member of a group of cationic channels belonging to the family of amiloride-sensitive degenerine sodium channels. Specifically, the Applicants have shown a new member that belongs to the well-characterized family of amiloride-sensitive degenerine sodium channels, which has been well-characterized in the art. (Canessa et al. (1993), Waldmann et al. (1995); Driscoll et al. (1991); Huang et al. (1994); Waldmann et al. (1996)). This complex family of ion channels demonstrates varied physiological roles. As a result of the characterization of this family of amiloride-sensitive degenerine sodium channels and the clear identification of the functional properties thereof, it is respectfully submitted that the identification of an additional member of this family inherently possesses a functional and well-established utility.

The Examiner is kindly asked to consider the case of, In re Kirk, 153 USPQ 48, 53 (CCPA 1967),which indicated that a disclosure of a compound that is similar to a compound having a known activity could be deemed to imply that the novel compound has a related specific activity. In re Kirk, 153 USPQ at 53. The Applicants have demonstrated that the biophysical and pharmacological properties of the ASIC channels of the invention are close to those of the proton-activated cationic channels described in the prior art references of Krishtal et al. (1991); Kovalchuk et al. (1990); and Konnerth et al. (1987). Consequently, the Applicants' ASIC channels have a specific pharmacological activity, which is similar to the activity of a known compound that has a demonstrated and well-established utility. Furthermore, the court in Nelson v. Bowler held that the identification of a specific pharmacological activity provides an immediate benefit and therefore satisfies the requirement of 35 U.S.C. § 101. Nelson v. Bowler, 206 USPQ 881, 883 (CCPA 1980). Courts have continuously recognized that when the prior art discloses a compound having a proven action, then a structurally similar compound may inherently possess the same utility. In re Brana, 34 USPQ2d 1436, 1442 (CAFC 1995). Moreover, it is well-established principal of law that pharmaceutical related inventions necessarily include the expectation of further research and development. Nelson, 206 USPQ at 883. The Court in Nelson v. Bowler stated that:

> Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to compact illness and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility.

The holding in Nelson v. Bower is applicable to this case. The Applicants have identified

a particular compound, namely protein channels contained within mammals, which are altered by any of a number of drugs including, for example, amiloride (a drug that blocks sodium/proton anti-port and has been used clinically as a potassium sparing diuretic). Consequently, the Applicants respectfully submit that the identification of channels, which are regulated by this drug clearly provides a demonstrated and well-established utility of pharmacological consequence.

It is respectfully submitted that the Applicants have identified naturally occurring proteins and DNA sequences which are known to be expressed in organisms. Logically, this organism would not produce the protein or express the DNA sequence unless it were advantageous to the organism. One skilled in the art would therefore recognize that the protein was inherently useful to the organism and as a result necessarily demonstrates inherent utility. The law has recognized that inherent utility or a utility which is obvious to persons skilled in the art "need not be specifically stated." Standard Oil v. Montedison, 212 USPQ 327, 343 (3d Cir. 1981). As a demonstration of this inherent utility, the Applicants' specification describes that the naturally occurring genes could be used for gene therapy in individuals who lack a functional ASIC gene.

Turning now to consideration of Brenner v. Manson, it is respectfully submitted that the aforementioned case is factually dissimilar to this application. Applicants respectfully submit that the utility of the compound produced by the method claimed in Brenner v. Manson was unknown, and therefore could not be said to have a specific benefit or a well-established utility. In contrast, the Applicants have demonstrated that the ASIC protein channels are directly effected by neurological compounds, such as amiloride. The Applicants have shown a channel which is sensitive to acid, and protons. It is well-known in the art that the stimulation of sensory neurons by acids accompanies

numerous painful inflammatory reactions. Specifically, the art has recognized that the pain caused by acids is interpreted as being mediated by the cationic channels presented at the level of the sensory neurons which are activated by protons. (Page 1, lines 15-18 of Applicants' specification). Consequently, the regulation of these channels and their sensitivity to acids and their role in mechanisms to relieve pain associated with acidity.

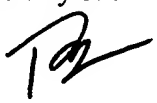
It is respectfully submitted that the current situation is analogous to In re Bergel, which involved compounds suitable for the treatment of cancer. Similarly, the Applicants have identified specific channels, which relate to the transmission and treatment of pain. The court in In re Bergel acknowledge that utility was found in the appellants progression toward the healing and curing of cancer. Similarly, the Applicants have made sufficient progress toward the goal of treating pain. In view of the foregoing, Applicants respectfully submit that the claimed invention clearly illustrates a specific and well-established utility for isolated, naturally occurring proteins associated with the tranmission of pain. The Applicants have particularly described the physiological and genetic characterization of these channels, as well as their regulation through pharmacological agents.

Amended Claims 1-3, 5, 11-13, 15, 17-24 and 26-29 have been rejected under 35 U.S.C. § 112, first paragraph. Applicants respectfully submit that as a result of the claim amendments and in light of the arguments set forth above these rejections are now obviated. Specifically, the Applicants have amended the claims to include sequence identifiers, as well as a percentage limitation of homology for the functionally equivalent derivatives. As a result, it is respectfully submitted that the specification provides a written description of the amended claims and that one skilled in the art would clearly recognize that the Applicants were in possess of the claimed

invention.

In view of the foregoing, Applicants respectfully submit that the claims are now in condition for allowance, which action is respectfully requested.

Respectfully submitted,



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